REMARKS

STATUS OF THE CLAIMS

Claims 1-2, 16-17, 19-22, 63, and 65-67 were pending in this application. Claims 1, 22, 63 and 65 have been amended. Claims 65-67 have been cancelled. New claims 68, 69, 70 and 71 have been added. Following entry of the amendments claims 1-2, 16-17, 19-22, 63, and 68-71 will be pending and at issue.

INTERVIEW SUMMARY

On October 12, 2006, a telephonic interview was conducted between the Examiner and the Applicant's representative, Antonia Sequeira. The parties discussed a possible amendment to claim 1 to overcome the rejections, and the Examiner indicated that the Applicant should be sure to provide an explanation of how any amendment made is enabling and how it overcomes the prior art.

SUPPORT FOR THE AMENDMENTS TO THE CLAIMS

Claims 1 and 63 have been amended recite "agonist-mediated receptor function." Support for the amendment can be found throughout the specification as filed, as described in detail regarding the rejections 35 U.S.C. § 112, first paragraph, below. New claims 68 and 69 have been added to recite agonist-mediated functions, such as mediation of adenylyl cyclase activity, mediation of G-protein receptor coupling, mediation of MAP kinase activation, mediation of inositol phosphate synthesis, and combinations thereof. Support for these claims can be found in the claims as filed and throughout the specification as filed, e.g., at Page 8, lines 13-23 ("Upon binding of the agonist, the receptor stabilizes in a conformation that favors contact with all activation of certain heterotrimeric G proteins. These include G_i G_i2, G_i3 and G_o. The G_i G protein alpha subunits serve to decrease the activity of the enzyme adenylyl cyclase, which lowers the intracellular levels of cAMP (a classic second messenger). The alpha subunits, and/or the beta gamma subunits of these G proteins also act to activate MAP kinase, open potassium channels, inhibit voltage gated calcium channels, and stimulate inositol phosphate

accumulation."), Page 9, lines 16-20 ("Alpha-2B adrenergic receptor molecule function or activity can be measured by methods known in the art. Some examples of such measurement include radio-ligand binding to the alpha-2B adrenergic receptor molecule by an agonist or antagonist, receptor-G protein binding, stimulation or inhibition of adenyly cyclase, MAP kinase, phosphorylation or inositol phosphate (IP3)."), etc. New claims 70 and 71 have been added to recite agonists, such as epinephrine, norepinephrine, clonidine, oxymetazoline, guanabenz, UK14304, BHT933 and combinations thereof. Support for these claims can be found in the claims as filed and throughout the specification as filed, e.g., Page 49, lines 4-7 ("Preferred agonists include alpha-2B adrenergic receptor agonists, such as for example, epinephrine, norepinephrine, clonidine, oxymetazoline, guanabenz, UK14304, BHT933 and combinations thereof."); Page 64, lines 12-15 ("In these experiments, cells were incubated with media alone or media containing agonist (10 μM norepinephrine) for 30 min and extensively washed, membranes prepared, and agonist-mediated inhibition of forskolin stimulated adenylyl cyclase activity was determined"), Table 3, etc.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claim 22 was rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite because the Examiner stated that the phrase "oligonucleotide" lacks proper antecedent basis. Applicants thank Examiner for pointing out this typographical error. Applicants have amended claim 22 to depend from claim 20, thereby correcting this error. Therefore, Applicants request withdrawal of this rejection as drawn to the amended claim.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1, 2, 16, 17, 19, 20-22, 63, and 65-67 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner found that the amendments made to the claims represent new matter. The Examiner noted that the Applicant teaches that the polymorphism showed altered or decreased

receptor coupling, but further noted that this is not a broad recitation that all ligand-binding function is decreased. Office Action, p. 3. Applicants have amended independent claims 1 and 63 to recite "establishing that an agonist-mediated receptor function of said alpha-2B-adrenergic receptor is reduced if said deletion polymorphism is present as compared to said agonist-mediated receptor function if said deletion polymorphism is absent."

The present specification describes the function of the alpha-2B adrenergic receptor in more detail, as follows:

> The alpha-2B adrenergic receptor is localized at the cell membrane and serves as a receptor for the endogenous catecholamine agonists i.e., epinephrine and norepinephrine, and synthetic agonists and antagonists. Upon binding of the agonist, the receptor stabilizes in a conformation that favors contact with all activation of certain heterotrimeric G proteins. These include G_i G_i2, G_i3 and G_o. The G_i G protein alpha subunits serve to decrease the activity of the enzyme adenylyl cyclase, which lowers the intracellular levels of cAMP (a classic second messenger). The alpha subunits, and/or the beta gamma subunits of these G proteins also act to activate MAP kinase, open potassium channels, inhibit voltage gated calcium channels, and stimulate inositol phosphate accumulation. The physiologic consequences of the initiation of these events include inhibition of neurotransmitter release from central and peripheral noradrenergic neurons.

Page 8, lines 13-23. Thus, the wild-type receptor couples with certain G proteins that serve numerous functions, including decreasing the activity of the enzyme adenylyl cyclase (thereby lowering intracellular cAMP).

The specification explains that agonist-mediated receptor function is reduced when the polymorphism is present. For example, the specification states that in one embodiment, in which an alpha-2B adrenergic receptor agonist is administered, the agonist "activates the alpha-2BAR molecule and G_i coupling results in inhibiting adenylyl cyclase, and decreased phosphorylation." Specification, p. 48, lines 10-12. The specification explains that the mutant alpha-2BAR showed "decreased inhibition of adenylyl cyclase (Figure 3A-C) as compared to the wild-type alpha-2BAR with insertion of three glutamic acids (IN301-303) at amino acid position 301 to 303 of SEQ ID NO: 7." *Id* at lines 12-15. The specification thus concludes that the "mutant alpha-2BAR has decreased receptor activity or function." *Id* at lines 15-16.

In addition, the specification includes working examples regarding evaluation of the consequences of the polymorphism on both ligand binding and also on receptor function. Specification, p. 62, lines 27-29. The specification explains that the functional consequences of the mutation are addressed by studies examining agonist-promoted inhibition of forskolin stimulated adenylyl cyclase activities that were carried out in cell lines expressing the wild-type and mutant receptors. Specification, p. 63, lines 18-21. These working examples involving adenylyl cyclase activities are described at pages 59-60 of the specification. As explained in the Results and Discussion of the examples, the "Del 301-303 receptor displayed less inhibition of adenylyl cyclase (23.4 ± 2.2%) compared to wild-type alpha 2BAR (28.5 ± 1.6%, $p<0.05$)," and "the polymorphic receptor had a greater EC_{50} (19.6 t 5.5 vs 7.9 ± 2.1 nM, $p<0.0I$)." *Id.* at lines 22-24. The results of these experiments are also presented in Table 3 at page 71 of the specification. Thus, the specification concludes that the mutant showed a decrease in agonist-mediated receptor function. *Id.* at lines 24-27.

Furthermore, this reduction in agonist-mediated function is illustrated with regard to the specification's description of receptor coupling. As explained in the portion of the specification cited above (Page 8, lines 13-23), upon binding of the agonist, the receptor stabilizes into a conformation that results in activation of certain G proteins that serve to decrease the activity of the enzyme adenylyl cyclase, which lowers intracellular levels of cAMP. Thus, agonist-mediated receptor function can be measured by examining G-protein receptor coupling, and a decrease in receptor coupling indicates reduced agonist-mediated receptor function. As explained in the specification and as the Examiner noted at Office Action, p. 3., a decrease in receptor coupling was observed the where the polymorphism was present, and this was noted a number of times in the specification. Specification at, e.g., page 9, lines 22-25 ("The DEL301-303 polymorphism also showed altered or decreased receptor coupling"), page 66, lines 13-16, page 56, lines 25-27, etc. Thus, this observed decrease in receptor coupling further indicates a reduction in receptor function for the mutant. Therefore, according to the specification, "agonist-mediated receptor function of said alpha-2B-adrenergic receptor is reduced if said

deletion polymorphism is present as compared to said agonist-mediated receptor function if said deletion polymorphism is absent," as claimed.

Accordingly, Applicants respectfully submit that the subject matter of the claims as amended was described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Thus, Applicants request withdrawal of this rejection as drawn to the amended claims.

Claims 1, 2, 16, 17, 19, 20-22, 63, and 65-67 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner's arguments were similar to those stated above regarding the lack of written description rejection. As stated above, the claim has been amended as stated above to recite "establishing that an agonist-mediated receptor function of said alpha-2B-adrenergic receptor is reduced if said deletion polymorphism is present as compared to said agonist-mediated receptor function if said deletion polymorphism is absent." As described above, descriptions in the specification indicating reduced agonist-mediated function in the mutated receptor along with working examples regarding adenylyl cyclase activities, receptor coupling, etc. are included in the specification at various locations, as described above.

Accordingly, Applicants respectfully submit that the subject matter of the claims as amended complies with the enablement requirement, so Applicants request withdrawal of this rejection as drawn to the amended claims.

The Examiner indicated that the Applicants overcame all previous prior art rejections (including for references cited in the prior Office Action, Jewell-Motz (Biochemisty, 1995, Vol. 34, pages 11946-11953) and Heinonen (The Journal of Clinical Endocrinology & Metabolism, July 1999)) with the amendments to the claims. The Applicants further note that the references (including Jewell-Motz and Heinonen) do not teach the elements of claims 1 and 63 as amended herein. Heinonen does not refer to any reduction in agonist-mediated receptor function or provide any working examples regarding this. Jewell-Motz examined the functional consequences of the mutation based on adenylyl cyclase assays. In the adenylyl cyclase assays,

the receptor with the 16 amino acid deletion appeared to be "fully functional" and the "maximal agonist-mediated inhibition of adenylyl cyclase was similar with the mutant receptors as compared to the wild-type." Jewell-Motz at p. 11949, first full paragraph. Jewell-Motz further noted that the "EC_{50} for inhibition with the deletion mutant was the same as that found with the wild-type receptor." *Id.* Jewell-Motz also found that the deletion did not alter G-protein coupling since the mutant receptor "displayed formation of the high-affinity agonist-receptor-G protein ternary complex as assessed in agonist competition studies performed in the absence of guanine nucleotide." *Id.* at 11953, first full paragraph. Jewell-Motz specifically concluded that the mutations examined involving the 16 amino acid deletion and substitution did not affect "receptor expression, agonist, or antagonist binding affinities, guanine nucleotide-sensitive formation of the high-affinity agonist-receptor-G protein complex, or functional coupling of the receptor to G_i." Jewell-Motz, Abstract. Thus, neither Jewell-Motz nor Heinonen teaches the element of "establishing that an agonist-mediated receptor function of said alpha-2B-adrenergic receptor is reduced if said deletion polymorphism is present as compared to said agonist-mediated receptor function if said deletion polymorphism is absent."

CONCLUSION

Withdrawal of the pending rejections and reconsideration of the claims are respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is invited to telephone Applicant's representative at (650) 335-7185.

Respectfully submitted,
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